

Methodological and Mechanistic Considerations on Duration-Dependent Pulsed Radiofrequency for Rheumatoid Arthritis [Letter]

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Dear editor

We read with great interest the excellent research recently published by Li et al exploring 1-, 2-, and 3-minute dorsal root ganglion (DRG) pulsed radiofrequency (PRF) for collagen-induced arthritis (CIA) rats.¹ While the study provides valuable preliminary data on duration-dependent PRF efficacy, this letter raises several methodological, mechanistic, and translational questions regarding the study design. Specifically, we focus on the single PRF treatment regimen, limitations of tail-flick pain testing, lack of transient receptor potential (TRP) causal verification, short observation period, and the uncharacterized safety profile of prolonged stimulation. Resolving these issues will further strengthen the reliability of their core conclusion that a 2-minute PRF is optimal for rheumatoid arthritis (RA).

First, the study adopted a fixed intervention scheme: four PRF sessions separated by 20-minute intervals on day 1 of week 9 after model establishment. However, the paper does not discuss the influence of treatment frequency or interval length on therapeutic outcomes. It remains unclear whether repeated PRF courses (eg, once weekly for 3 weeks) could produce longer-lasting anti-arthritis effects, and whether the proposed 2-minute optimal duration remains consistent under different treatment frequencies. Consequently, this single-session intervention design may limit the translational generalizability of the clinical parameter recommendations, and further studies exploring multi-session protocols are warranted to validate the durability of the observed effects.

Second, the sole pain assessment indicator was tail-flick latency, which cannot specifically evaluate hind ankle joint pain—the primary lesion site of CIA rats. Tail-flick detects thermal spinal reflex pain rather than mechanical allodynia, swelling-induced hyperalgesia or weight-bearing dysfunction specific to RA. The significant improvement in tail-flick latency cannot fully represent relief of arthritic joint pain; supplementary behavioral tests are necessary to validate the analgesic conclusion.²

Third, while the study observed a significant downregulation of synovial TRP ankyrin 1 (TRPA1) and TRP vanilloid 1 (TRPV1) expression following PRF intervention, it stops short of establishing a causal mediation. The authors hypothesize that PRF alleviates RA injury specifically by inhibiting these TRP channels; however, without mechanistic validation—such as the use of pharmacological inhibitors, agonists, or gene knockout models—this targeted pathway remains speculative. Critically, given that PRF was applied to the dorsal root ganglia rather than directly to the joint tissue, it cannot be excluded that the reduced synovial TRP expression is merely a secondary, downstream consequence of the broadly attenuated joint inflammation (eg, secondary to reduced neurogenic inflammation), rather than a direct therapeutic mechanism of PRF.³ Interestingly, even in their previous study,⁴ the causal relationship between PRF, TRP downregulation, and pain relief was not functionally dissected, suggesting a consistent gap in this research direction. Incorporating such functional assays would substantially strengthen their mechanistic conclusions.

Fourth, a 14-day observation window is methodologically insufficient to evaluate a chronic, progressive condition like RA. In the CIA model, progressive cartilage erosion and synovial proliferation typically evolve over 8–12 weeks; therefore, the current short-term follow-up cannot reliably distinguish between transient inflammatory suppression and sustained structural joint protection.⁵ Consequently, whether the 2-minute PRF intervention genuinely prevents or delays irreversible joint damage in the late stages of RA remains to be established. While the authors rightfully acknowledged the limitations of both the tail-flick assay and the brief observation period in their discussion, we respectfully argue that until these methodological limitations are adequately addressed, declaring a 2-minute duration as the optimal standard may be premature.

Furthermore, while the authors reported no statistical difference in efficacy between the 2-minute and 3-minute PRF groups, they did not address the potential safety implications of prolonged 3-minute stimulation. Extended radio-frequency exposure to the DRG carries a theoretical risk of inducing unintended neuronal thermal injury or neurotoxicity, as prolonged electrical field application may produce cumulative thermal effects even at the so-called “non-thermal” 42°C setting.^{6,7} Given the absence of detailed neural histological evaluations in the current study, the safety profile of the 3-minute protocol remains uncharacterized. Future studies should therefore incorporate systematic histological assessments of DRG neuronal integrity (eg, Nissl staining or electron microscopy) to establish the safety profile of prolonged PRF protocols before any duration can be definitively recommended as optimal.

We fully recognize the novelty of this work in optimizing PRF stimulation duration for RA, and we put forward complementary experimental suggestions to address the above limitations: (1) add multiple-session PRF subgroups to explore the interaction between treatment intervals and duration; (2) adopt von Frey test and weight-bearing asymmetry to quantify joint-specific pain; (3) employ pharmacological inhibitors or TRPA1/TRPV1 knockout models to verify pathway causality; (4) extend the post-intervention observation period to 8–10 weeks to adequately assess long-term chondroprotective efficacy; (5) conduct DRG neuronal histological assessments to evaluate the safety profile of prolonged 3-minute PRF stimulation.

We welcome the authors’ response to these concerns, and trust that addressing these methodological and mechanistic questions through further experimental investigations will further enrich the translational value of this otherwise important preclinical work.

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Disclosure

The authors declare there are no conflicts of interest in this communication.

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